Testosterone deficiency, the unrecognised consequence of the opioid epidemic in men

Janine David, GP[1] and Associate Specialist in Andrology;[2] **Mike Kirby,** Editor[3]
1. Porthcawl Medical Centre, UK; 2. Princess of Wales Hospital, Bridgend, UK; 3. *Trends in Urology and Men's Health*

Testosterone deficiency resulting from chronic opioid use can have a profound effect on health and quality of life, but it often goes unrecognised and untreated. Here the authors review the problem and discuss strategies for management.

The headline that opioid deaths in the USA, mainly occurring in young people, reached over 100 000 in the past 12 months prompted this review.[1]

This death toll apparently equals more than the total caused by car accidents and gun deaths. Importantly, it is much more common in men than women. Data from the Centres for Disease Control and Prevention (CDC) show that overdose deaths rose 28.5% in the 12 months ending April 2021. This partly explains the increase in available organ body parts to transplant clinics.[2]

The fatalities will have had lasting repercussions on families and, perhaps even more poignantly on friends, because most of them have occurred among people aged 25–55 years. The rise in deaths was mainly caused by synthetic opioids and aggravated by the widespread use of fentanyl, which may be added surreptitiously to other illegally manufactured drugs to enhance their potency.

In the UK the situation is also very worrying. According to 2020 registrations in England and Wales, there were 4561 deaths related to drug poisoning (equivalent to a rate of 79.5 deaths per million people); this is 3.8% higher than the number of deaths registered in 2019 (4393 deaths; 76.7 deaths per million).[3] More than twice as many deaths occurred in men compared with women: among males there were 109.7 drug poisoning deaths registered per million in 2020 (3108 registered deaths), compared with 49.8 deaths per million among females (1453 deaths).[3] Statistics are based on the year of death registration. However, because of death registration delays, around half of these deaths will have occurred in the previous year (2019) and the majority

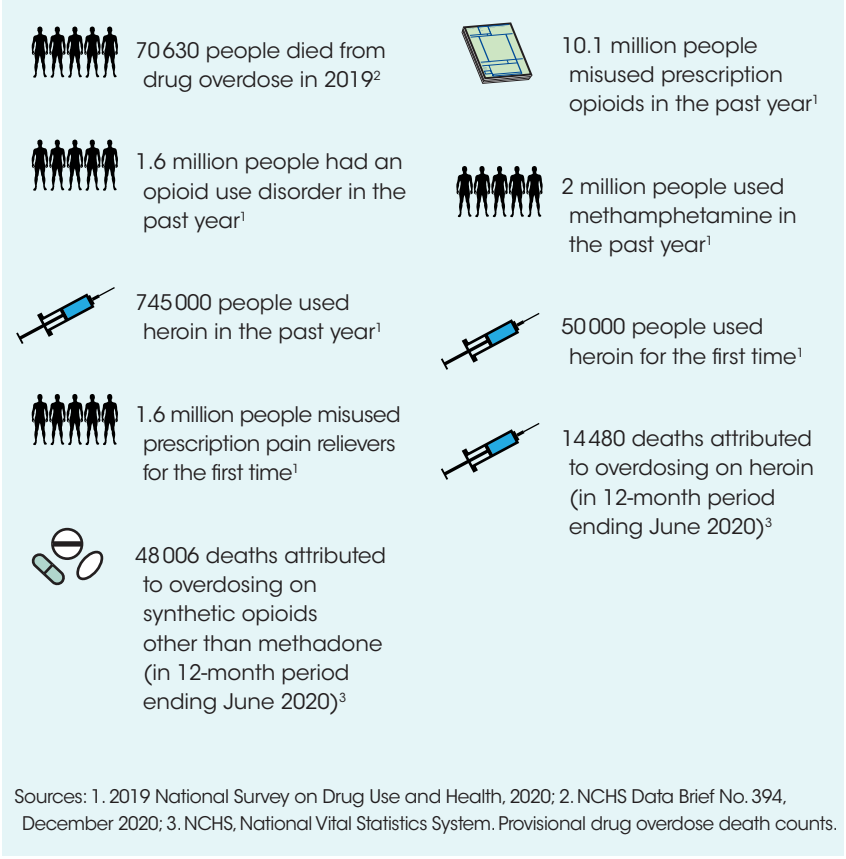
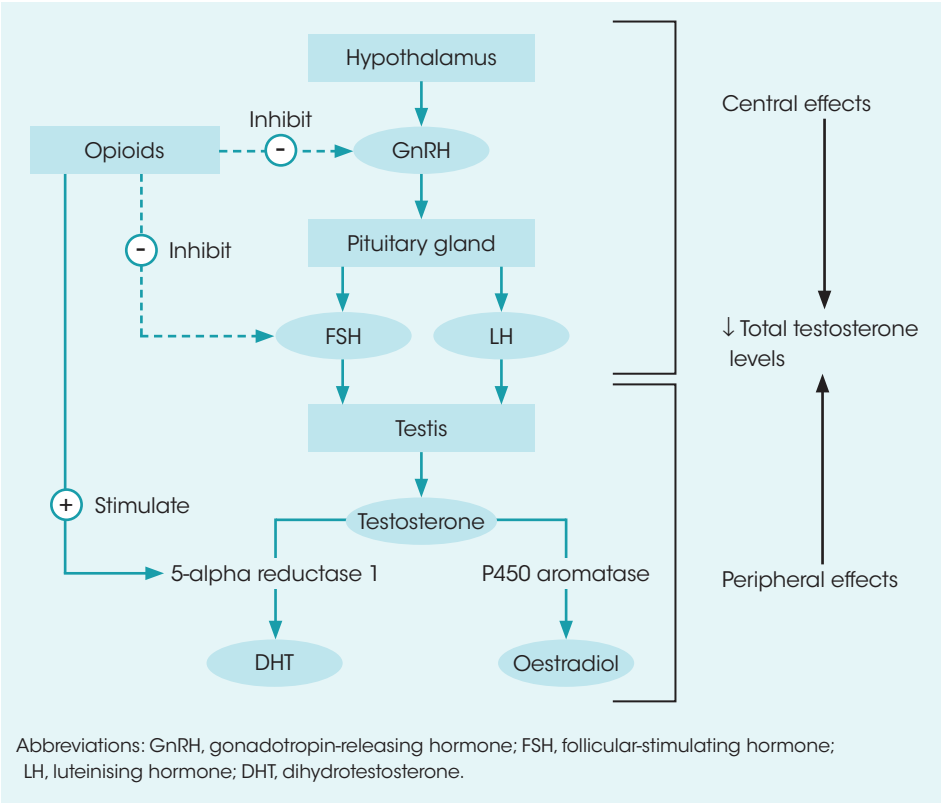


Figure 1. The opioid epidemic in the USA by numbers.[13] Adapted from www.hhs.gov/opioids/sites/default/files/2021-02/opioids-infographic.pdf



Abbreviations: GnRH, gonadotropin-releasing hormone; FSH, follicular-stimulating hormone; LH, luteinising hormone; DHT, dihydrotestosterone.

Figure 2. Pathogenesis of opioid-induced hypogonadism.[14] Adapted from Coluzzi F, Billeci D, Maggi M, *et al.* Testosterone deficiency in non-cancer opioid-treated patients. *J Endocrinol Invest* 2018;41:1377–88

will have occurred before the coronavirus (COVID-19) pandemic in the UK.

Managing pain in primary care

Managing pain in primary care can be very difficult. Achieving an understanding of how pain is affecting a person's life and those around them and knowing what is important to the person is the first step in developing an effective care and support plan. This recognises and treats a person's pain as valid and unique to them. Pain that lasts for more than three months is known as chronic or persistent pain. In the UK the prevalence of chronic pain is uncertain, but appears common, affecting perhaps one-third to one-half of the population. Chronic pain that is caused by an underlying condition (for example, osteoarthritis, rheumatoid arthritis, ulcerative colitis, endometriosis) is known as chronic secondary pain. Where the cause of the pain is unclear it is called chronic primary pain.

Chronic pain is one of the most common GP consultations and up to 50% of adults in the UK have chronic non-cancer pain.[4] In addition, pain affects more people in the USA than diabetes, heart disease and cancer combined;[5] chronic pain is very costly on both an individual and a societal level.[6]

The NICE guideline on primary and secondary chronic pain makes recommendations for treatments that have been shown to be effective in managing chronic primary pain. These include exercise programmes and the psychological therapies CBT and acceptance and commitment therapy (ACT). Acupuncture is also recommended as an option. People with chronic primary pain should not be started on commonly used drugs, including paracetamol, non-steroidal anti-inflammatory drugs, benzodiazepines or opioids. This is because there is little or no evidence that they make any difference to people's quality of life, pain or psychological distress, but they can cause harm, including possible addiction.[7]

Opioids are very good analgesics for acute pain and pain at the end of life, but there is little evidence that they are helpful for long-term pain. Despite this, they are widely prescribed for this reason and opioid prescribing more than doubled from 1998 to 2018. This has been referred to as an opioid epidemic in the UK, similar but not on the same scale as the opioid crisis in the USA.[8]

Most opioids are μMOP agonists; they are classified according to receptor binding, and opioid receptors are ubiquitous throughout the body.

- Agonists, *eg* morphine, codeine, fentanyl, heroin, oxycodone
- Partial agonists, *eg* buprenorphine, tramadol, tapentadol[9]

Impact of illicit use of prescription opioids around the world

In the USA (Figure 1), New Zealand and Australia, the illicit use of prescription opioids outpaces that of heroin.[10] From 1996 to 2012, Oxycontin sales in the USA increased from $48 million to $2.4 billion. Using data from death certificates, the CDC estimates that 100306 people died from drug overdose between April 2020 and April 2021, compared with 78056 deaths reported the year prior.[1] In July 2021 four drug companies agreed to pay $26 billion to resolve opioid lawsuits.[11,12]

Impact of opioids on the male endocrine system

The endocrine system can be severely affected by chronic opioid treatment, leading to a decrease in total testosterone levels and opioid-induced hypogonadism (Figure 2). Opioids depress the secretion of hormones at different levels of the hypothalamic–pituitary–gonadal axis, and generally

increase levels of growth hormone, thyroid-stimulating hormone and prolactin, but there are conflicting reports on the effects of opioids on arginine, vasopressin and adrenocorticotropic hormone. In addition, opioids can lead to the development of hypogonadism by directly inhibiting gonadotropin-releasing hormone (GnRH) through the μ-opioid receptor, reducing libido and causing erectile dysfunction (ED), bone loss and/or infertility.[14]

The impact occurs rapidly, often within one week, and the highest risk appears to be among patients receiving significant dosages for longer than one month. Use of the more potent opioids are more likely to cause a greater risk of hypogonadism, but the effects seem to be reversible after a few days of withdrawal. As one might expect, long-acting opioids have a greater risk compared with short-acting drugs. There is a significant correlation between increased dosage and development of opioid-induced androgen deficiency (OPIAD).[14]

A retrospective US cohort study evaluated data from men aged 26–79 years (n=81; mean age 51 years; median/mean BMI 29/31kg/m^2) who had a diagnosis of chronic pain (defined as pain lasting for >3 months without any aetiology that allowed for definitive or curative treatment) and were on a stable dosage of opioid therapy for ≥3 months, of whom 46 were hypogonadal and 35 were not. After controlling for daily opioid dosage and BMI, men on long-acting opioids had 4.78 times greater odds of becoming hypogonadal than men on short-acting opioids (95% CI 1.51–15.07; p=0.008). In total, 74% (n=34/46) of men receiving long-acting opioids were hypogonadal compared with 34% (12/35) of men using short-acting opioids exclusively. After controlling for daily opioid dosage and duration of action of opioid, BMI was also found to be significantly associated with hypogonadism; for every unit increase of BMI, patients had an additional 13% higher odds of being hypogonadal (95% CI 1.03–1.24; p=0.006). The model also showed that for every 10mg increase in daily opioid dose, patients had an additional 2% greater chance of being hypogonadal, but this was not significant (95% CI 0.99–1.05; p=0.29).[15]

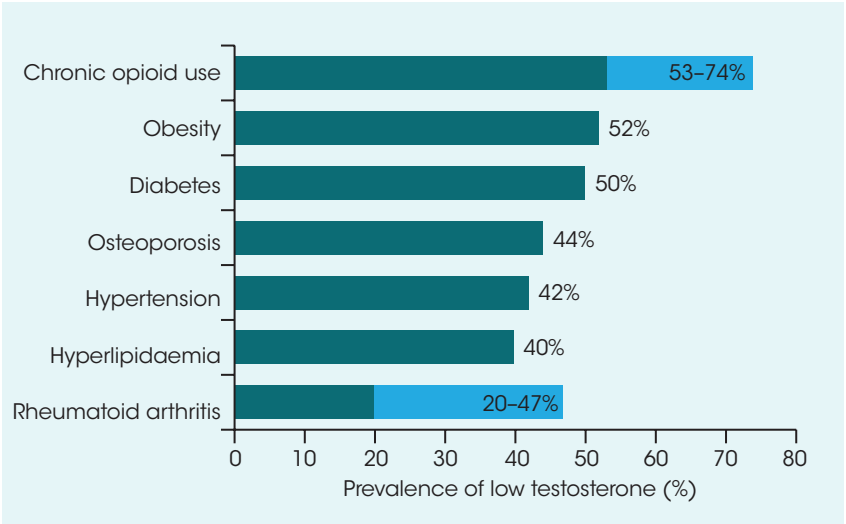


Figure 3. Prevalence of low testosterone among chronic opioid users and men with other conditions[19]

In another retrospective US cohort study, which evaluated data from men aged 18–80 years (n=1159) who had chronic non-cancer pain and were on a stable regimen of a single opioid for ≥90 days (n=190 received a long-acting opioid, n=969 received a short-acting opioid), hypogonadism was noted in 69.2%, 60.8%, 52.1%, 50.4%, 42.9%, 35.5% and 34.2% of patients receiving fentanyl, methadone, morphine, oxycodone, hydromorphone, codeine and hydrocodone, respectively. Results for each opioid were analysed with reference to hydrocodone because the bivariate results indicated that patients using hydrocodone were least likely to be androgen-deficient; moreover, it was the largest group. Fentanyl (OR 25.73; 95% CI 2.82–234.97), methadone (OR 7.33; 95% CI 3.29–16.33) and oxycodone (OR 3.15; 95% CI 1.87–5.33) were all associated with higher odds of hypogonadism than hydrocodone. Morphine was also associated with elevated odds of hypogonadism compared with hydrocodone (OR 2.40; 95% CI 0.92–6.28); however, this result was not statistically significant. The highest odds of hypogonadism appeared to be associated with those opioids that maintain very stable serum drug levels. The conclusions drawn from this study suggest that before commencement of opioid therapy or modification of existing opioid therapy, patients should undergo testosterone testing.[16]

The prevalence of OPIAD ranges from 19% to 86%, with most studies reporting an overall prevalence higher than 50%, confirming the significant impact of opioids in reducing testosterone levels.[14,17,18] Figure 3 shows the prevalence of low testosterone among chronic opioid users and men with other conditions.[19]

A systematic review and meta-analysis of testosterone suppression in opioid users concluded that testosterone level was suppressed in men with regular opioid use regardless of opioid type and found a mean testosterone difference of 5.7nmol/L between opioid users and controls. Opioids were found to affect testosterone levels differently in men than women, and testosterone was not found to be suppressed in studies examining opioid-using women.[20]

Rubenstein *et al.* studied 1585 men receiving long-acting opioids and discovered that 57% were diagnosed with testosterone <12nmol/L.[21]

Opioids can induce several hypogonadism-related signs and symptoms, including sexual dysfunction, mood impairment and fatigue, obesity and cardiovascular disease, osteoporosis and sexual dysfunction.

Why more deaths in men than women?

Could suppression of normal testosterone levels be a contributing cause, via increases in anxiety, depression, metabolic syndrome, cardiovascular disease, fall risk and difficulties with sexual activity?

Depression

Depressive symptoms seem to be related to the dosage and duration of treatment, exacerbated by OPIAD. As well as opioids affecting testosterone levels, testosterone may also be involved in regulation of endogenous opioid activity. A registry study of male opioid users with low testosterone found that sexual function and mood improved significantly over a 12-month course of testosterone gel administration.[22]

Most studies suggest that lower testosterone levels are associated with depressive symptoms. Furthermore, testosterone replacement therapy (TRT) has been shown to improve depressive symptoms in most men. This could be due to the fact that testosterone is a modulator of GABA receptors and inhibits 5-HT3 receptors centrally. Men with depressive symptoms and testosterone deficiency syndrome should be given a trial of TRT, as TRT alone may improve clinical symptoms of depression. Furthermore, men already on SSRIs may experience further improvement in depressive symptoms after initiating TRT.[23]

Depression, anxiety and decreased quality of life are the most common psychopathological conditions in young hypogonadal men. Thirty-nine young male patients with congenital hypogonadotropic hypogonadism (CHH) and 40 age-matched healthy males were enrolled in a Turkish study.[24] The impact of TRT on patients' anxiety and depression levels, sexual function and quality of life were assessed before and after six months of treatment using valid and reliable scales, including the 36-Item Short Form Health Survey (SF-36), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI) and Arizona Sexual Experiences Scale (ASEX). Patients with CHH had significantly higher scores for BDI, BAI, and ASEX than the control subjects at baseline (p=0.011, p=0.036, p<0.001, respectively). The ASEX and BDI scores significantly improved after the TRT (p<0.001 for both). When compared with the control group, treatment-naïve hypogonadal patients had more severe symptoms of sexual dysfunction, anxiety, depression, and worse quality of life. After six months of TRT, there were observed improvements in the above parameters, suggesting that low endogenous levels of testosterone might be related to the increased incidence of psychological symptoms.

Sexual dysfunction

Chronic pain itself causes sexual dysfunction and can be a non-organic cause of ED, and men with OPIAD have reported poorer pain control and hyperalgesia. Lower testosterone levels lead to ED and loss of libido, and sex inertia resets the reproductive axis to a lower level of activity inducing a secondary hypogonadism by reducing LH production.[25]

Weight gain and metabolic syndrome

Pain, physical limitations and depression lead to decreased activity and increased eating, and opioids increase appetite. The association between decreased testosterone, obesity and metabolic syndrome is bidirectional and increases the risk of cardiovascular disease.[26]

Cardiovascular side-effects

A study using the UK General Practice Research Database found an increased risk of myocardial infarction in 1.7 million patients with at least one prescription for an opioid to treat chronic non-cancer pain between 1990 and 2008.[27]

Bone health

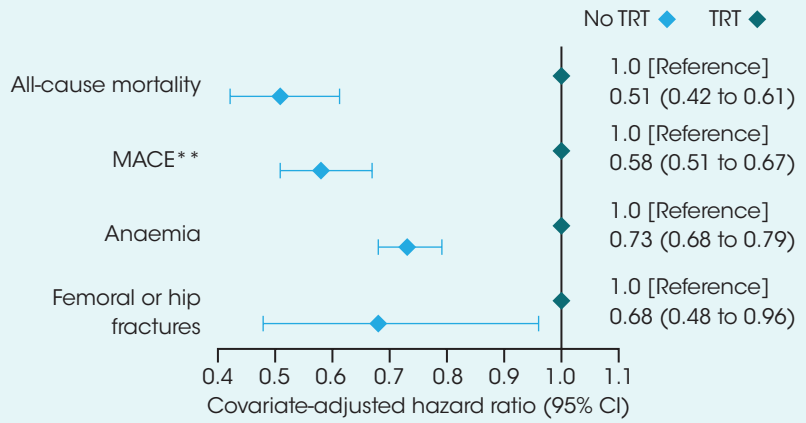
Osteoporosis is a consequence of testosterone deficiency and opioid treatment is associated with a 50–60% increased risk of osteoporotic fractures. The mechanism is due to a direct effect on bone formation by impairing osteoblastic activity. It appears that patients on tramadol, which has less MOP affinity, have a lower incidence of osteoporosis. The fall risk is increased due to the central nervous system effects of opioids such as dizziness.[28]

Impact of treatment with testosterone

So, would identifying and treating these men with testosterone make a difference to mortality, other adverse health outcomes and pain?

Mortality and other adverse health outcomes

TRT significantly decreases all-cause mortality and other adverse health outcomes in men with opioid-induced hypogonadism versus TRT non-use. A cohort study involved men using long-term opioid therapy with low testosterone levels (<10.4nmol/L) under the care of Veterans Health Administration facilities in the USA from 1 October 2008 to 30 September 2014. Male patients with HIV infection, gender dysphoria or prostate cancer, or who received TRT in 2008 were excluded. In total, 21 272 long-term opioid users (mean [SD] age 53 [10] years) were included for analysis, of whom 14 121 (66.4%) received TRT and 7151 (33.6%) did not. After adjusting for covariates, opioid users who received TRT had significantly lower all-cause mortality (HR 0.51; 95% CI 0.42–0.61) and incidences of major adverse cardiovascular events (MACE) (HR 0.58;



*Adjusted for age, race/ethnicity, marital status, BMI, co-pay requirement, zip code poverty level, and baseline status of the following clinical conditions: indications for pain, chronic pain conditions, use of glucocorticoids, congestive heart failure, cancers, coronary artery disease, hypertension, diabetes, hyperlipidaemia, liver disease, chronic kidney disease, stroke or transient ischaemic attack, dementia, depression, bipolar disease, substance use disorder, alcohol dependence, psychosis, and use of antipsychotic medications. **MACE: incident cases (new occurrence) of myocardial infarction or thrombotic stroke or death.

Figure 4. Likelihood of adverse outcomes after six years of follow-up in men with opioid-induced hypogonadism on chronic opioid therapy (n=21 272)*[29]

95% CI 0.51–0.67), anaemia (HR 0.73; 95% CI 0.68–0.79) and femoral or hip fractures (HR 0.68; 95% CI 0.48–0.96) during the six-year follow-up period, compared with their counterparts without a TRT prescription (Figure 4).[29]

Pain

A randomised trial[30] of testosterone replacement in men with opioid-induced androgen deficiency also showed a positive result on pain, sexual desire, body composition and quality of life. Men were recruited, aged 18–64 years, with chronic non-cancer pain, with a morning testosterone <12.1nmol/L. Eighty-four men were randomised, 43 men to AndroGel 1% and 41 men to placebo. This was a single-site investigation with assessment at baseline and week 14 with hormone assays, self-reported pain and quantitative sensory testing, sexual function and quality of life. Changes in body composition were reported.[30] Compared with men assigned to the placebo arm, those assigned to testosterone replacement experienced greater improvements in pressure and mechanical hyperalgesia, sexual desire and role limitation due to emotional problems. Testosterone administration was also associated with an improvement in body composition. There were no between-group differences in changes in self-reported pain. In conclusion, in men with opioid-induced androgen deficiency, testosterone administration improved pain sensitivity, sexual desire, body composition and aspects of quality of life. The authors also concluded that testosterone therapy improved pain sensitivity to a number of noxious painful stimuli, confirming its antinociceptive role, but there is need for larger randomised trials of longer duration to further evaluate the efficacy of testosterone in chronic pain syndromes.

Identifying men in the community

Opioid-induced hypogonadism is a lesser known but highly prevalent adverse effect in patients on long-term opioid therapy. Narcotics have both central and peripheral effects causing reduced serum testosterone levels. Clinicians should look for these lesser-known adverse consequences and assess them clinically based on their signs and symptoms. Testosterone replacement therapy is a viable option for managing symptomatic males.[31] The Endocrine Society[32] advises that, when assessing men for testosterone deficiency, this should include a general health evaluation to exclude systemic illness, eating disorders, excessive exercise, sleep disorders, and use of recreational drugs and certain medications (*eg* opioids or high-dose glucocorticoid therapy) that affect testosterone production or metabolism. The British Society for Sexual Medicine[33] also advises screening for testosterone deficiency in all men on long-term opiate, anticonvulsant or antipsychotic medication.

Summary

OPIAD is common and can impair satisfactory pain relief. OPIAD also impairs sexual activity, mood, bone metabolism and is a risk factor for cardiovascular disease and obesity.

Guidelines support screening for testosterone deficiency in this situation. Consideration should be given to screening for testosterone deficiency prior to an opioid prescription, to provide a baseline. From a clinical point of view, the effect is reversible and if the opioid is removed, the deficiency is reversed, usually within a month.

Wherever possible consider alternative pain management strategies, as per NICE guidance, but if treatment is necessary consider using an opioid with a lower MOP affinity such as buprenorphine or tramadol, and enquire about relevant low testosterone symptoms, with testosterone measurements at subsequent follow-up. Current evidence suggests testosterone replacement might be beneficial and synergistic with analgesics to improve pain control in hypogonadal men.

OPIAD can have a profound effect on health and quality of life, and it can hinder a clinician's ability to effectively

treat chronic pain and manage complex comorbidities, but it often goes unrecognised and untreated.

Declarations of interest

Janine David has received funding from Bayer, Besins, Coloplast and Ferring. Mike Kirby has received funding for research, conference attendance, lecturing and advice from the pharmaceutical industry including Astellas, Pfizer, Takeda, Bayer, Besins, MSD, BI, Lilly, GSK, AZ and Menarini. No funding was associated with the publication of this article.

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